Specific collagen peptides in osteoporosis management: Unraveling therapeutic potential through expert perspectives and scientific insights

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Abstract

Background: Osteoporosis, characterized by reduced bone mineral density, increased fracture risk and impaired quality of life, remains a significant global health concern. Collagen, serving as the foundational structure for bone mineralization, emerges as a crucial component in the armamentarium against osteoporosis.

Objective: This expert opinion captures insights from a panel of experts, highlighting the role of specific collagen peptides in the management of osteopenia and osteoporosis.

Methods: To achieve this consensus, a group of 13 orthopedics experts from across India came together in Mumbai on 15th October 2023 to review the existing clinical data and discuss the role of specific collagen peptides in the management of osteopenia and osteoporosis.

Results: Collagen, as the fundamental structural component for bone mineralization, emerges as a critical element in osteoporosis management. Specific Collagen Peptide, being a small chain of amino acids, is easily absorbed from the GI tract and, via the circulatory system, reaches the bone marrow, where it activates the formation of osteoblast from bone marrow stem cells plus also inhibits the activity of osteoclast through an increase in the OPG/RANKL ratio. Specific Collagen Peptides (SCP) demonstrated enhancements in Bone Mineral Density (BMD) by 4.2% in the spine and 7.7% in the femoral neck, coupled with alterations in bone turnover markers in 12 months. A clinically relevant increase in BMD was observed in the 4-year follow-up study; no fractures were reported by any patients, and no drug interaction and tolerability issues were noted in the study.

Conclusion: The consensus among experts underscores the necessity of integrating once-a-day oral 5 gm specific collagen peptide supplementation (Nutra with a drug-like action) into standard osteoporosis management. SCP, with its dual action on both osteoblast and osteoclast (Along with Calcium and vitamin D), can be used stand-alone or can be used for its synergistic action when used along with anti-resorptive (Bisphosphonate/denosumab) as well as anabolic (teriparatide) treatment.

Keywords: Administration, oral, dietary supplements, bone density / drug effects, collagen / administration & dosage, postmenopause / blood

1. Introduction

Osteoporosis results from a series of events leading to significant bone loss and fragile, easily fractured bone. Approximately 61 million people in India have osteoporosis. This silent disease affects many women compared to men, i.e., one in three females compared to one in eight males suffer from osteoporosis [1]. Fracture incidence is lower in men because of higher peak bone density, less bone loss during aging, and fewer falls. Osteoporosis is one of the most common diseases affecting elderly people, leading to more fractures, pain, and reduced mobility and quality of life. More than 250,000 people in India sustain a hip fracture every year. More than 4.5 million women above the age of 60 years in India have a fractured spine [2].
Early diagnosis and treatment of osteoporosis is essential to minimize fracture risk. Diagnosis is usually done by evaluating the T-score obtained by Dual X-ray absorptiometry (DEXA) scan and Fracture Risk Assessment Tool (FRAX®). Bone turnover markers (BTMs), i.e., type I collagen C-telopeptide (CTX) and procollagen type I N-propeptide (PINP), are helpful in assessing patient compliance and efficacy of therapy. The mainstay of treatment for osteoporosis includes dietary changes, regular weight-bearing exercises, calcium and vitamin D supplementation, and pharmacologic treatment, mainly with antiresorptive or anabolic agents [9].

Hormone therapies, selective estrogen receptor modulators (SERMs), or bisphosphonates are available for treatment. However, some of these drugs (e.g., Bisphosphonates) are often poorly tolerated and have serious side effects such as Osteonecrosis of the jaw (ONJ) and atypical femoral fractures (AFFs) [5]. In addition, treatment inertia is a major problem, as only 12.9% to 72.0% of all osteoporosis patients worldwide use treatment options within the first 2 years [3]. To overcome these safety and compliance issues, there is a need for nutraceutical options like specific collagen peptides. The results of clinical studies have shown that the administration of specific collagen peptides has anabolic (Bone forming) and anti-catabolic (Prevents breakdown of bone) effects [6]. A clinical study demonstrated that the simultaneous intake of collage peptides, calcium, and vitamin D improves bone mineral density (BMD) [7]. Hydrolyzed Collagen may serve as an effective supplement for preventing bone loss by significantly enhancing the organic substance content of bone. This could be explained by a downregulation of the production of pro-inflammatory molecules such as interleukins-1b and -6 and tumor necrosis factor-α. Because these cytokines, in particular, are responsible for the upregulation of receptor activator for nuclear factor kappa-B ligand (RANKL) for osteoclast recruitment, this may explain the noteworthy impairment of bone loss [8-10].

Specific collagen peptides, also called collagen hydrolysates produced by the hydrolysis of collagen, have also been shown to have high oral bioavailability and have a place in the management of osteoporosis [7, 11-16]. Collagens represent 30% of the total protein mass in the body [17]. They are the major structural element in the extracellular matrix of all connective tissues, including bone, where they represent about 80% of the total protein [18]. Spindle or plate-shaped crystals of hydroxyapatite are found between and around collagen fibers, oriented in the same direction as collagen fibers [19-23]. While the mineral content mainly determines bone stiffness and rigidity, collagens provide skeletal toughness and flexibility. Type I collagen comprises approximately 95% of the entire collagen content of bone. Bone matrix, unlike other connective tissues, possesses the unique ability to become calcified.

Type I collagen molecules are involved in the mechanical properties (Toughness, tensile strength, compression, etc.) of bone [20, 21]. Collagen peptide compounds exert their beneficial effect on bone by affecting bone remodeling and mineralization of the bone matrix, promoting the proliferation and differentiation of pre-osteoblasts while reducing the maturation of osteoclasts [3]. Several preclinical studies performed in mice and rats support this notion and suggest that orally administrated CPs increased BMD, as well as the compositional and biodynamic characteristics of vertebrae [3]. Ovariectomized rats are a US FDA-approved model for studying any drug in osteoporosis management. Studies have shown that specific collagen peptides increase longitudinal bone growth in rats and increase bone mass in both growing rats following treadmill training as well as mature rats. It also inhibits bone loss in ovariectomized rats and prevents bone loss in estrogen-deficient rats by reducing the levels of proinflammatory cytokines [18, 19].

2. Need for Expert Opinion

Though certain nutraceuticals have shown benefits in patients with osteoporosis, the management is hindered by insufficient awareness among physicians and patients of the potential benefits of evidence-based nutraceuticals, particularly specific collagen peptides, as part of osteoporosis treatment. To address these issues, a practical guidance document is of paramount importance.

3. Methodology

The Nutraceuticals expert group meeting included 13 Orthopaedicians across India. They participated in the expert group meeting on 15th October 2023 to discuss the role of specific collagen peptides and their use in Osteoporosis management. The discussion was based on existing literature, including clinical data.

The objective was to develop a document of expert opinion that would help the medical fraternity to address the unmet need in the management of OP with specific collagen peptides. It is a compilation of clinical data, the mechanism of action, and its position in therapy. The utilization of specific collagen peptides can improve OP management, potentially reducing fracture risk and improving patient outcomes.

4. Panel discussion

4.1 Role of collagen

Clinical evidence: In bone, collagen plays an essential role in force transmission and tissue structure maintenance and determines the amount of mineral deposition. Thus, the capacity of bone to resist mechanical forces and fractures depends not only on the quantity of bone tissue (Mineralization) but also on its quality (Organization of the collagen framework) [20, 23]. During aging, there is a reduction in bone mechanical strength and elasticity, which contributes to the occurrence of osteoporotic fractures [24]. In postmenopausal osteoporosis, the volume fraction of minerals and the relative amounts of mature and immature collagen crosslinks are affected by the tissue turnover rate, thus contributing to bone fragility [20].

4.1.2 Specific Collagen Peptide

Specific Collagen Peptides (SCP) consist of different small chains of amino acids optimized for site-specific (Bone cells - osteoblast, osteoclast) physiological benefits. The peptides are derived from a highly controlled production process of collagen, which is determined by hydrolyzation conditions. The molecular weight signifies protein hydrolysis and strongly correlates with the peptides' bioavailability and bioactivity. Peptides with lower molecular weights exhibit greater potency compared to higher molecular weight ones due to their enhanced ability to traverse the intestinal barrier and exert biological effects. Additionally, shorter-chain peptides demonstrate increased effectiveness in influencing physiological processes as they are less prone to gastrointestinal hydrolysis, unlike long-chain peptides [25]. Fig 1. Depicts the molecular weight distribution of various collagen peptides. The molecular weight distribution of various specific collagen peptides is distributed in ranges from < 500 kDa, 500-1500 kDa, 1500-3500 kDa, 3500-7500 kDa, and above.
Specific collagen peptide influences bone health through multiple mechanisms (Fig. 2). The amino acid chain of specific collagen peptide - Aspartic Acid-Glycine-Glutamic-A Alanine (Asp-Gly-Glu-Ala) initiates bone marrow cell differentiation into osteoblasts by interacting with the α2 β1 integrin receptor on cell membranes. SCP also stimulates osteoblast differentiation, bone matrix formation, and osteogenic markers by activating signaling pathways like ERK/MAPK. SCP can induce Insulin-like growth factor 1 (IGF1) production, which consequently activates a calcium-sensing receptor and, in turn, exerts an anabolic effect on bone. SCP could affect osteoclasts by increasing the OPG/RANKL ratio, potentially reducing bone resorption. Further research is necessary to understand the exact mechanism [26].

Expert opinion
All the experts agreed that Specific Collagen Peptide was a missing piece in the management of osteopenia and osteoporosis. The expert panel agreed that collagen has a major role in tissue structure maintenance and bone mineralization. Though calcium supplementation is quite common amongst middle-aged and elderly patients, many people still suffer from osteoporosis and osteopenia. The experts discussed the role of collagen as part of the bone structure. Anatomically, bone is a mixture of mineral crystals held in an organic collagen matrix. On their own, the mineral crystals would be extremely brittle and prone to break. Like a bridge is built out of concrete and steel, collagen in the bones is essential for bone flexibility and elasticity. It is important to keep the skeletal system healthy.

The experts opined that specific collagen peptide is necessary in the management of osteoporosis and osteopenia, as they show action on both, i.e., osteoclasts as well as osteoblasts. As per previous clinical studies, specific collagen peptide are safe and well.

4.2. Clinical benefits
### 4.3. Position in therapy

**Algorithm**

![Algorithm](https://www.orthopaper.com)

**Expert opinion:** The experts suggested incorporating Specific Collagen Peptide as an adjuvant therapy (Fig. 3) alongside calcium, vitamin D, and existing pharmacological treatments in the management of osteopenia and osteoporosis. SCP, with its dual action on both osteoblast and osteoclast (along with Calcium and vitamin D), can be used stand-alone or can be used for its synergistic action when used along with anti-resorptive (Bisphosphonate/denosumab) as well as anabolic (Teriparatide) treatment.

### 4.4. Dosage & duration

**Clinical evidence:** According to the clinical studies mentioned previously, the dosage proven to be effective is 5 grams daily, and the duration of use should span over a minimum period of 12 months to 4 years [14].

**Expert opinion**

The experts recommended that the daily oral dosage and duration of Specific Collagen Peptide in the management of osteopenia and osteoporosis should be 5 g for minimum of 12-months to 4 years period.

### 4.5. Expert Statements and Prospects
**Table:**

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Expert Opinion Statements</th>
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<tbody>
<tr>
<td>1.</td>
<td>There are gaps in the management of osteopenia and osteoporosis due to treatment inertia, safety, and compliance concerns with the current drugs.</td>
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<tr>
<td>2.</td>
<td>To overcome this gap, there is a role for a bone-specific nutraceutical that is effective and safe for osteopenia and osteoporosis.</td>
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<tr>
<td>3.</td>
<td>Specific Collagen Peptide (SCP) serves as the structural foundation for bone mineralization and represents a crucial component in the management of osteoporosis.</td>
</tr>
<tr>
<td>4.</td>
<td>SCP improved bone Mineral Density (BMD) and altered bone turnover markers (PINP &amp; CTX) without any recorded osteoporotic fractures within 4 years of treatment.</td>
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<td>5.</td>
<td>In osteoporosis management, specific collagen peptides have a long-lasting anabolic effect (Minimum three months) after the discontinuation of therapy.</td>
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<td>6.</td>
<td>Collagen supplementation should be integrated into the clinical algorithm for osteoporosis management for superior patient outcomes.</td>
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<tr>
<td>7.</td>
<td>SCP once daily 5-gram oral supplementation should be prescribed for a minimum of 12 months to 4-year period.</td>
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<tr>
<td>8.</td>
<td>SCP, with its dual action on both osteoblast and osteoclast (Along with Calcium and vitamin D), can be used stand-alone or can be used for its synergistic action when used along with anti-resorptive (bisphosphonate/denosumab) as well as anabolic (Teriparatide) treatment.</td>
</tr>
<tr>
<td>9.</td>
<td>SCP is a missing piece in the management of osteoporosis.</td>
</tr>
<tr>
<td>10.</td>
<td>SCP is safe and well tolerated in patients with osteoporosis, with no reported adverse drug interaction and tolerability issues in the clinical studies.</td>
</tr>
<tr>
<td>11.</td>
<td>The experts favored non-vegetarian sources for obtaining high-quality collagen, suggesting limitations in obtaining good collagen from vegetable sources.</td>
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**5. Conclusion**

The experts established the role of specific collagen peptide in the management of osteoporosis. Collagen shows its role in bone health, serving as the fundamental structural framework for bone mineralization and demonstrating anabolic as well as anti-catabolic action. The consensus among experts strongly advocates for integrating collagen supplementation into standard osteoporosis treatment regimens, addressing existing gaps, and offering a more comprehensive therapeutic approach. The complementary nature of SCP with pharmacological therapy signifies the potential for synergy in optimizing osteoporosis management.

**6. Acknowledgment**

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**7. Conflict of Interest:** Not available.

**8. Financial Support:** Not available.

**9. References**


13. Ichikawa S, Morifuji M, Ohara H, Matsumoto H, Takeuchi Y, Sato K. Hydroxyproline-containing dipeptides and tripeptides quantified at high...
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